Remarks

Responsive to the Office Action dated March 9, 2005, Applicants request consideration of the following remarks. A reconsideration of the present application respectfully is requested. Claims 10-11 and 17-20 have been canceled. As such, claims 1-9 and 12-16 are pending and under consideration. Each of these claims is believed to be in condition for allowance and such favorable action is requested.

103 Rejections

35 U.S.C. § 103(a) Rejections

To establish a *prima facie* case of obviousness, three criteria must be met:

1) there must be some suggestion or motivation to modify the reference or to combine reference teachings;

2) there must be a reasonable expectation of success; and

3) the prior-art references must teach or suggest all the claim limitations.

Moreover, the teaching or suggestion, and the reasonable expectation of success must be found in the prior art and not be based on applicants' disclosure. *See* MPEP § 706.02(j), § 2142, and § 2143.

Claims 1-5 have been rejected under 35 U.S.C. 103(a) as being unpatentable over by Sugi et al. (The American Journal of Gastroenterology, Vol. 91, No. 5, 927-934, 1996) (the "Sugi reference"). As the Sugi reference neither teaches nor suggests a method for precluding a diagnosis of irritable bowel syndrome and other noninflammatory etiologies if a sample does not contain an elevated level of endogenous lactoferrin, Applicants traverse the rejection.

Claim 1 recites a method for substantially precluding a diagnosis of irritable bowel syndrome and other noninflammatory etiologies by determining that a fecal sample does

not contain an elevated level of endogenous lactoferrin. The Sugi reference does not teach or suggest substantially precluding a diagnosis of irritable bowel syndrome and other noninflammatory etiologies by determining a fecal sample does not contain an elevated level of endogenous lactoferrin. The Sugi reference merely teaches using fecal lactoferrin as a marker for disease activity in inflammatory bowel disease.

Examiner contends that the "maker (sic) for inflammatory diseases would obviously preclude the detection of non-inflammatory events." This is not the case. **Lactoferrin is detectable in subjects with IBD, healthy persons as well as subjects with irritable bowel syndrome.** Thus, in order to preclude a diagnosis of IBS, it would be necessary to determine the level fecal lactoferrin in subjects with IBS (a non-inflammatory etiology). The level of fecal lactoferrin in subjects with IBS is not determined in the Sugi reference. Furthermore, Examiner has stated that the cited references are silent as to the measurement of lactoferrin in non-inflammatory disorders (See Office Action dated 3/9/05, page 6). A person of skill in the art could not develop a qualitative assay for differentiating IBD from IBS without determining the level of fecal lactoferrin in subjects with IBS. This level is needed to define a level of fecal lactoferrin to target a cut-off of the development of a diagnostic assay.

As there is no motivation or suggestion for determining the level of lactoferrin in subjects with IBS, it is not possible to for the Sugi reference to teach or suggest a level of fecal lactoferrin to determine the level of fecal lactoferrin needed to preclude a diagnosis of IBS. As the Sugi reference neither teaches nor suggests a method for substantially precluding a diagnosis of irritable bowel syndrome and other noninflammatory etiologies by determining a fecal sample does not contain an elevated level of endogenous lactoferrin, Applicants request withdrawal of the 103(a) rejection of claim 1. As claims 2-5 depend directly or indirectly from claim 1, Applicants request withdrawal of the rejection of these claims as well.

Claims 6-9 and 12-16 have been rejected under 35 U.S.C. 103 (a) as being unpatentable over Sugi in view of Peen et al. Gut, 1993, 34, 56-68 (the "Peen reference). With respect to claims 6-9, as stated above, the Sugi reference teach or suggest substantially precluding diagnoses of irritable bowel syndrome and other noninflammatory etiologies by determining a fecal sample does not contain an elevated level of endogenous lactoferrin as claimed by independent claim 1.

The Peen reference also does not teach nor suggest substantially precluding a diagnosis of IBS and other noninflammatory etiologies by determining a fecal sample does not contain an elevated level of endogenous lactoferrin. Rather, the Peen reference teaches measuring human immunoglobulins to lactoferrin in serum samples, not lactoferrin itself, from patients with ulcerative colitis and primary sclerosing chloangitis. The ELISA method described in Peen uses human lactoferrin immobilized on a 96-well plate for the capture of human autoantibodies to lactoferrin. Following the first incubation with human serum, immunonglobulins to lactoferrin will bind to the lactoferrin coated wells. The second incubation allows for the binding of anti-human immunoglobulin conjugate to bound antibody. Following the addition of substrate, the optical density is read and a positive result is indicated of the presence of anti-lactoferrin human immunoglobulins, **not endogenous lactoferrin**. A Western blot analysis is then used to show the auto-antibodies are binding to human lactoferrin. There is no teaching or suggestion that diagnoses of IBS and other noninflammatory etiologies can be precluded because a sample does not contain an elevated level of lactoferrin.

As neither the Sugi reference nor Peen reference teach or suggest substantially precluding a diagnosis of IBS and other noninflammatory etiologies by determining a fecal sample does not contain an elevated level of endogenous lactoferrin, Applicants request

withdrawal of the rejection of claims 6-9 as they depend directly or indirectly from independent claim 1.

With reference to claims 12-16, independent amended claim 12 is drawn to an assay determining whether an enzyme-linked antibody bound sample contains an elevated level of lactoferrin as compared to a reference value for health control subjects, wherein the optical density of the enzyme-linked antibody bound sample is read at 450 nm, wherein if said enzyme-linked antibody bound sample contains an elevated level of endogenous lactoferrin, a diagnosis of irritable bowel syndrome is substantially precluded. As neither the Sugi reference nor the Peen reference teach nor suggest a diagnostic assay for determining whether a fecal sample contains an elevated level of endogenous lactoferrin as compared to a reference value for healthy control subjects by determining the optical density of an enzyme-linked antibody bound sample at 450 nm, Applicants traverse the rejection.

The Sugi reference does not teach or suggest determining the optical density of an enzyme-linked antibody bound sample at 450 nm. Rather, the Sugi reference teaches measurement of fecal lactoferrin. The Sugi reference teaches an enzyme reaction test and measurement of color development with a microplate colorimeter at 510/630 nm, and not 450 nm. The specification of the present application has described a method of substantially precluding diagnoses of IBS and other non-inflammatory etiologies if a test result is considered positive for lactoferrin when the optical density (OD)of a sample is greater than 0.200 at 450 nm for a specimen. The teachings in the Sugi reference do not teach or suggest determining the optical density of a readable sample at 450 nm to determine if the sample contains an elevated level of lactoferrin wherein if the level is elevated, a diagnosis of IBS is substantially precluded. There is no motivation or reasonable expectation of success that an elevated level of lactoferrin shown by the optical density of a readable sample at 450 nm substantially precludes the

diagnoses of IBS and other non-inflammatory etiologies as the Sugi reference does not even discussing measuring the level of lactoferrin in a patient with IBS. It is not possible to determine the optical density of a positive result to differentiate a patient with IBD from a patient with IBS if the measuring the level of lactoferrin in a fecal sample of a patient with IBS is not taught or suggested.

The Peen reference also does not teach or suggest measurement of optical density of an enzyme-linked antibody bound sample at 450 nm. The Peen reference teaches high frequencies of IgG anti-lactoferrin antibodies, not lactoferrin itself, in serum samples from patients with ulcerative colitis and primary sclerosing chloangitis. The Peen reference differs from independent claim 12 in that it detects IgG anti-lactoferrin antibodies, not lactoferrin in serum samples as claimed by claim 12 of the present application.

As the Sugi reference and the Peen reference neither teach nor suggest a diagnostic assay for determining whether a fecal sample contains an elevated level of endogenous lactoferrin as compared to a reference value for healthy control subjects by determining the optical density of an enzyme-linked antibody bound sample at 450 nm, Applicants request withdrawal of the 103(a) rejection of claim 12. As claims 13-16 depend directly or indirectly from claim 12, Applicants request withdrawal of the 103(a) rejection as to these claims as well.

The present application is believed to be in condition for allowance, and Applicants request that a timely notice of allowance be issued for this case. Should any unresolved issues remain in the case, please feel free to contact the undersigned at the phone number listed below.

Respectfully submitted.

Jean M. Dickman

Jean M. Dickman
Reg. No. 48,538

JMD:nlm

SHOOK, HARDY, & BACON L.L.P.
2555 Grand Boulevard
Kansas City, MO 64108-2613
TEL 816.474.6550 + FAX 816.421.5547